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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/957,709	10/24/1997	HOLLY HOGREFE	1486/41363CP	2438

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EXAMINER	
RAMIREZ, DELIA M	
ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 11/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/957,709	HOGREFE ET AL.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17,46,59-66,77-79,85,87-91,95,97* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17, 46, 59-66, 77-79, 85, 87-91, 95, 97* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Claims 17, 46, 59-66, 77-79, 85, 87-91, 95, 97 are pending.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/13/2004 has been entered.

Applicant's amendment of claims 17, 46, 85, 87, 90, amendments to the specification, and submission of a new sequence listing in electronic and paper form, in a communication filed on 9/13/2004 are acknowledged.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Objections

1. Claim 17 is objected to due to the recitation of "one subunit is a P. furiosus protein selected from: a protein encoded.....; and a protein having a sequence...". To be consistent with commonly used claim language, it is suggested that the term be amended to recite "one subunit is a P. furiosus protein selected from the group consisting of: a protein encoded.....; and a protein having a sequence...". Appropriate correction is required.

2. Claim 46 is objected to due to the recitation of "amino acid sequence consisting of at least one of SEQ ID NO: 19 and 71". To be consistent with commonly used claim language, it is suggested that the term be amended to recite "amino acid sequence consisting of at least one sequence selected from the group consisting of SEQ ID NO: 19 and 71". Appropriate correction is required.

3. Claim 63 is objected to due to the recitation of "amino acid sequnce of SEQ ID NO: 71". The claim should be amended to recite "amino acid sequence of SEQ ID NO: 71". Appropriate correction is required.

4. Claims 90, 91 and 97 are objected to due to the recitation of "A protein extract of claim X". Since the protein extract has already been defined in a previous claim, it is suggested that the term be amended to recite "the protein extract of claim X". Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claim 85 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claim 85 is indefinite in the recitation of "wherein the protein is at least 39% similar to SEQ ID NO: 71" because as written one cannot determine what the meaning of the term "similar" is within the context of the claim. If the term similar refers to sequences, i.e. sequence similarity, it is noted that this term can have different meanings in the art. The term "sequence similarity" can be interpreted as "sequence identity", which is calculated based solely on the number of exact matches between two sequences, and can also be interpreted as "sequence homology", which is calculated taking into consideration conservative substitutions. Thus, even if the claim were to recite "39% sequence similarity", one of skill in the art cannot reasonably determine the basis for this % calculation. Furthermore, the specification does not provide a definition for the term "sequence similarity". For examination purposes, it will be assumed that the term reads "wherein the protein is at least 39% sequence identical to the polypeptide of SEQ ID NO: 71". Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claim 85 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 85 (as interpreted) is directed to a protein comprising the amino acid sequence of SEQ ID NO: 73, wherein said protein is at least 39% sequence identical to the polynucleotide of SEQ ID NO: 71. See Claim Rejections under 35 USC 112, second paragraph for claim interpretation. While Applicants point to the teachings of page 19 of the specification as support for the protein claimed, it is noted that the specification only indicates that "a sequence similarity of approximately 39% suffices to positively identify a dUTPase activity that can act as a PEF". Thus, in view of what has been disclosed in the specification as pointed out by Applicants, one cannot reasonably conclude that there is adequate support for the claimed proteins. Also, the Examiner has been unable to locate support for the claimed protein in other sections of the specification. Therefore, there is no indication that proteins comprising SEQ ID NO: 73 and having at least 39% sequence identity to the polypeptide of SEQ ID NO: 71 were within the scope of the invention as conceived by Applicants at the time the application was filed. Accordingly, Applicants are required to cancel the new matter in the response to this Office Action.

10. Claim 85, 87-91 and 97 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in

the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection has been discussed at length in Paper No. 33, mailed on 5/6/2003, as well as in the Advisory Action mailed on 4/20/2004.

11. In regard to claim 85, Applicants argue that the 14 amino acids in SEQ ID NO: 73 have been shown to have sequence similarity to a putative uridine binding motif, and submit that the specification teaches that the putative uridine binding motif is conserved in Ψ synthetases, dCTP deaminases, and dUTPases. Since dUTPase activity is related to PEF function, the structural element identified as SEQ ID NO: 73 is related to PEF function. Applicants further argue that claim 85 has been amended to recite an additional structural limitation, i.e. 39% similarity to SEQ ID NO: 71.

12. Applicant's arguments in regard to claim 85 have been fully considered but are not deemed persuasive to overcome the instant rejection. As admitted by Applicants, the putative uridine-binding motif of SEQ ID NO: 73 is found in different enzymes, e.g. Ψ synthetases, dCTP deaminases, and dUTPases. Thus, even if one were to conclude that any dUTPase would also have polymerase enhancing activity, the presence of this motif alone cannot be construed as an structural element which is responsible for the activity recited, i.e. polymerase enhancing factor (PEF) activity, since it can also be found in other enzymes which have not been shown to possess PEF activity. The addition of an additional structural limitation, while reducing the number of species claimed in the genus, is not deemed sufficient to be representative of all members of the genus of proteins claimed since there is no teaching in the specification as to which structural elements in the polypeptide of SEQ ID NO: 71 are responsible for PEF activity or even dUTPase activity. No information has been provided in regard to the structural elements in the polypeptide of SEQ ID NO:71 which can be modified to create a structural homolog having 39% sequence identity to the polypeptide of SEQ ID NO:71 and still display PEF activity, as required. Thus, there is no disclosed correlation between the structural elements recited and the function

required sufficient to show that applicants were in possession of the claimed invention at the time of filing.

13. In regard to claims 87-91 and 97, Applicants argue that whether or not the specification discloses isolation of a T. thermophilis dUTPase or its amino acid structure is irrelevant since claim 87 is directed to a protein extract and not to a specific protein or its structure. Since the specification has described a PCR enhancing protein extract comprising purified proteins from T. thermophilis and at least one protein in that extract with dUTPase activity, it is Applicant's contention that the claims comply with the written description requirement.

14. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection of claims 85, 87-91 and 97. The examiner agrees that the claims are not directed to a single protein or its amino acid structure. However, it is noted that the protein extract/composition claimed requires that at least one of the proteins be a T. thermophilis dUTPase. Claims 87-89 require a genus of T. thermophilis dUTPases having any structure, claims 90-91 require that the genus of T. thermophilis dUTPases be detected by an antibody specific for the protein of SEQ ID NO: 71, and claim 97 requires a genus of T. thermophilis dUTPases having any structure and a genus of T. thermophilis polypeptides of any function wherein said polypeptides of any function have a molecular weight of 24 KDa. It is reiterated herein that while it is acknowledged that the specification discloses the determination of dUTPase activity in a T. thermophilis cell extract and the detection in a Western blot of a protein in that cell extract using an antibody against the P. furiosus protein P45 of SEQ ID NO: 71, the specification fails to disclose the structural characteristics required in any T. thermophilis dUTPase such that a composition comprising said dUTPase would have PCR enhancing characteristics, or the structural elements in the polypeptide of SEQ ID NO: 71 which are associated with dUTPase activity and PCR enhancing activity. Also, it is noted that claim 97, as written does not require a T. thermophilis dUTPase having a molecular weight of 24 KDa.

While a sufficient written description of a genus of polypeptides may be achieved by a recitation of a representative number of polypeptides defined by their amino acid sequence or a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus, in the instant case, either (1) there are no recited structural features (claims 87-89), or (2) the recited structural features (claims 90-91), i.e. "can be bound by an antibody specific for the polypeptide of SEQ ID NO:71", do not constitute a substantial portion of the genus as the remainder of any polypeptide comprising said structural elements is completely undefined and the specification does not define the remaining structural features for members of the genus to be selected. Many structurally unrelated polypeptides are encompassed by these claims. The specification only discloses a single species of the claimed genus which is insufficient to put one of ordinary skill in the art in possession of all attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

15. It is noted that adding the limitations of claims 90 and 97 to claim 87 may obviate the instant rejection.

16. Claims 85, 87-91 and 97 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polypeptide of SEQ ID NO: 71 (156 amino acids), and a composition comprising said polypeptide, does not reasonably provide enablement for (1) a polypeptide having polymerase enhancing factor activity comprising the amino acid sequence of SEQ ID NO: 73 (14 amino acids) and having at least 39% sequence identity to the polypeptide of SEQ ID NO: 71, (2) a composition/protein extract comprising any T. thermophilis dUTPase, (3) the composition/protein extract of (2) wherein the T. thermophilis dUTPase can be detected with an antibody specific for the polypeptide of SEQ ID NO: 71, (4) the composition/protein extract of (2) or (3) further comprising a thermostable

DNA polymerase, or (5) the protein extract/composition of (2) further comprising a protein of any function which is approximately 24 KDa. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. This rejection has been discussed at length in Paper No. 33, mailed on 5/6/2003, as well as in the Advisory Action mailed on 4/20/2004.

17. In regard to claim 85, Applicants argue that the 14 amino acids in SEQ ID NO: 73 have been shown to have sequence similarity to a putative uridine binding motif, and submit that the specification teaches that the putative uridine binding motif is conserved in Ψ synthetases, dCTP deaminases, and dUTPases. Since dUTPase activity is related to PEF function, the structural element identified as SEQ ID NO: 73 is related to PEF function. Applicants further argue that claim 85 has been amended to recite an additional structural limitation, i.e. 39% similarity to SEQ ID NO: 71.

18. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection of claim 85. As indicated above, the putative uridine-binding motif of SEQ ID NO: 73 is found in different enzymes, e.g. Ψ synthetases, dCTP deaminases, and dUTPases. Thus, even if one were to conclude that any dUTPase would also have polymerase enhancing activity, the presence of this motif alone cannot be construed as an structural element which is responsible for the activity recited, i.e. polymerase enhancing factor (PEF) activity, since it can also be found in other enzymes which have not been shown to possess PEF activity. The addition of an additional structural limitation is not deemed sufficient to enable all members of the genus of proteins claimed since there is no teaching in the specification as to which structural elements in the polypeptide of SEQ ID NO: 71 are responsible for PEF activity or even dUTPase activity. No information has been provided in regard to the structural elements in the polypeptide of SEQ ID NO:71 which can be modified to create a structural homolog having 39% sequence identity to the polypeptide of SEQ ID NO:71 and still display PEF activity, as required. It is noted that the genus of polypeptides having at least 39% sequence identity to the

polypeptide of SEQ ID NO:71 (156 amino acids) is extremely large as this limitation would allow up to 95 amino acids to be substituted with 19 different amino acids or up to 95 deleted (95 = 156x61/100). Even if this genus is limited by the requirement of also comprising SEQ ID NO:73, the number of species in the genus is still extremely large. Therefore, testing the extremely large number of polypeptides encompassed by the claim would require undue experimentation. Also, it is noted that while one could argue that the claimed polypeptides can be isolated by using structural homology, the art clearly teaches the unpredictability of accurately determining function based solely on structural homology, and teaches examples of how even one amino acid substitution can result in a different function. Witkowski et al. (Biochemistry 38:11643-11650, 1999) teaches that one amino acid substitution transforms a β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl synthase activity. Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) teaches that two naturally occurring Pseudomonas enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Broun et al. (Science 282:1315-1317, 1998) teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform a hydrolase to a desaturase. Thus, in view of the teachings of the specification, the lack of knowledge as to a structure/function correlation, and the state of the art in regard to isolating proteins of similar function based solely on structural homology, one of skill in the art cannot reasonably conclude that the specification enables the full scope of the claimed invention.

19. In regard to claims 87-91 and 97, Applicants argue that the Examiner's position in regard to the potentially large number of antibodies which can bind to the polypeptide of SEQ ID NO:71 which do not have dUTPase activity is inconsistent with Applicant's results. According to Applicant's, if the antibody is so non-specific, one would expect to see numerous bands on a Western blot. In addition, Applicants argue that it was experimentally determined that the polypeptide of SEQ ID NO: 71 is a dUTPase and not

a dCTPase. Furthermore, according to Applicants, even if the antibody were to recognize both dCTPases and dUTPases, one of skill in the art would only have to distinguish between two proteins to identify a dUTPase. Applicants further submit that they have use antibody selection to identify T. thermophilis proteins which possess dUTPase activity and point to specific sections of the specification where a T. thermophilis protein extract was characterized as having dUTPase activity and detection of a 24 KDa band in that protein extract with an antibody specific for the polypeptide of SEQ ID NO:71. Applicants also argue that the specification discloses protein extracts where a thermostable DNA polymerase is added and state that making extracts from T. thermophilis or other cell extracts is well known in the art.

20. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the instant rejection. The Examiner acknowledges the amendments made to the claims, which are now limited to protein extracts/compositions comprising at a minimum (1) a genus of T. thermophilis dUTPases which have PCR enhancing capabilities, (2) a genus of T. thermophilis dUTPases which have PCR enhancing capabilities which can be detected by antibodies specific to the polypeptide of SEQ ID NO:71, or (3) a genus of T. thermophilis dUTPases which have PCR enhancing capabilities and a genus of T. thermophilis proteins of any function having a molecular weight of 24 KDa. However, as indicated above, the specification is silent in regard to (a) the structural elements required in any T. thermophilis dUTPase such that it has PCR enhancing activity, (2) the structural elements in the polypeptide of SEQ ID NO:71 which are associated with dUTPase activity and PCR enhancing activity, and (3) the function/structure of any T. thermophilis polypeptide which is 24 KDa. It is reiterated herein that the protein extract of claim 97 requires a genus of polypeptides of <u>any</u> function which are 24 KDa in addition to the genus of T. thermophilis dUTPases. The examiner agrees that the specification teaches a protein extract comprising T. thermophilis proteins wherein at least one of the proteins has dUTPase activity, wherein said protein having dUTPase activity has a molecular weight of 24 KDa and can be detected by an antibody specific for the polypeptide of SEQ ID NO:71. It is noted however that the claims, as

written, are not limited to such protein extract or a composition comprising said protein extract. Also, it has never been the Examiner's contention that the polypeptide of SEQ ID NO:71 is a dCTPase. It is clear from the specification that further characterization of that polypeptide shows it is most likely a dUTPase. However, in view of the fact that (1) the specification teaches that based on structural homology, the polypeptide of SEQ ID NO:71 could have been annotated as a dCTPase, and (2) an antibody against the polypeptide of SEQ ID NO:71 can potentially recognize a dCTPase since the epitope corresponding to that antibody may be one shared with a dCTPase due to the structural homology taught in the specification, there is the potential for that antibody to detect dCTPases in a protein extract. Since, there is (1) no evidence suggesting that dCTPases have PCR enhancing activity, and (2) no teaching as to which epitopes in the polypeptide of SEQ ID NO: 71 are associated with dUTPase activity, determining whether any protein which is detected by that antibody has dUTPase activity and the ability to enhance PCR would require undue experimentation. In regard to arguments that an antibody specific for the polypeptide of SEQ ID NO:71 was able to detect a 24 KDa protein from a protein extract containing proteins from T. thermophilis, it is reiterated herein that there is no limitation in the claims, including claim 97, which indicates that the T. thermophilis dUTPase has a molecular weight of 24 KDa. Thus, one cannot reasonably conclude that the specification enables the full scope of the claims.

21. It is noted that adding the limitations of claims 90 and 97 to claim 87 may obviate the instant rejection.

Double Patenting

22. Claims 17, 46, 59-66, 77-79, 85, 87-91, 95, and 97 remain rejected under the judicially created doctrine of double patenting over claims 1, 5-9, 13-20, 23-24, 26-34 and 40-41 of U.S. Patent No. 6,183,997. This rejection has been discussed at length in Paper No. 25, mailed on 2/27/2002.

23. Applicants have indicated that if the instant claims are found allowable, a terminal disclaimer will be filed. Since a terminal disclaimer has not yet been filed and no arguments have been presented pointing out disagreements with the Examiner's contentions, the double patenting rejection is maintained for the reasons of record.

Conclusion

24. No claim is in condition for allowance

25. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 872-9306. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

26. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

27. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (571) 272-0928. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
November 11, 2004

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP ~~1800~~ 1600